REMARKS

Applicant respectfully requests reconsideration. Claims 26-48 were previously pending in this application. No claims are amended herein. As a result, claims 26-48 are still pending for examination with claims 26 and 38 being independent claims. No new matter has been added.

Rejection Under 35 U.S.C. 112

Claims 26-48 have been rejected under 35 U.S.C. 112, first paragraph, as lacking written description.

The written description requirement can be met "even if every nuance of the claim is not explicitly described in the specification" particularly since Applicants are not required to recite information that is well known in the art. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986). One objective of the written description requirement is "to put the public in possession of what the applicant claims as the invention". MPEP 2163(I). Applicant has met this objective by disclosing the structure and function of the claimed genus of immunopotentiating oligonucleotides. The public was already in possession of phosphorothioate containing oligonucleotides. Applicant has taught in the specification that such oligonucleotides, regardless of their ability to produce antisense effects are useful for promoting cell mediated and local immune responses. Accordingly, the written description requirement for the claimed methods is met in view of the teaching in the specification and that which was already known in the art at the time of filing relating to oligonucleotides.

Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 26-48 have been rejected under 35 U.S.C. 112, first paragraph, as lacking enablement. Specifically the Examiner has dismissed Applicant's arguments in response to Crooke et al because seven additional references had been cited in prior office actions to support the state of the art regarding phosphorothioate analogs and that not all phosphorothioate analogs are immunostimulatory. However, Applicant had previously addressed each of these references. The

references were not mentioned in the last office action and were thus not addressed again by Applicant. Applicant hereby addresses these references below.

Allison et al. (Molecular Immunology 28: 279-284, 1991) was cited to support the conclusion that the scope of the claims is not enabled because the "data provided in the specification is not commensurate in scope with the claims, which are drawn to methods of stimulating an immune response using any phosphorothioate oligonucleotide analogs." Applicant's prior arguments were dismissed because, according to prior office actions, the specification only teaches the use of *one* oligonucleotide, ISIS 2105. Applicant disagrees. The specification describes the use of a class of molecules. The specific Examples in the specification describe data using ISIS 2105. However, working examples are not required. As such, MPEP 2164.02 states "[f]or a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art would expect the claimed genus could be used in that manner without undue experimentation" and that "lack of working examples or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement". Applicant is not required to provide a working example for each and every species in order to enable the genus.

Ratajczak et al. (PNAS USA 89:11823-11827, 1992) was cited as teaching that the "administration of sequence specific sense, antisense, and control phosphorothioate oligonucleotides to mice result in different responses depending on the sequence administered" (page 11825, third full paragraph, lines 16-27). Ratajczak et al was also cited to support the assertion that the "induction of splenomegaly and stimulation of B-lymphocyte proliferation in mice injected with phosphorothioate oligos occurs unpredictably in a manner that is dependent on the nucleotide sequence of the phosphorothioate oligonucleotide analogs". Applicant respectfully disagrees. Evaluation of splenomegaly and stimulation of B lymphocyte proliferation is one way of measuring a humoral immune response. A cell-mediated immune response may be evaluated, for instance, by measuring production of inflammatory cytokines such as IL-2, IFNγ, and TNFβ. Applicant has demonstrated efficacy of a phosphorothioate oligonucleotide analog in both antibody production and cytokine production. As stated previously, in the interest of furthering prosecution Applicant previously limited the claims to cell-mediated immune responses. The efficacy of the

phosphorothioate oligonucleotide analog in eliciting a cell-mediated immune response has been demonstrated in the Examples.

The Examiner had stated a broad conclusion that the unpredictability of the invention was known or widely accepted in the art at the time the instant application was filed. The references supporting this assertion were provided to show that non-antisense oligonucleotides do not produce a particular response. However, if the prior art had shown a stimulation of cell mediated immunity that was due to the backbone modification as opposed to an antisense effect the invention would not be novel. Applicant's discovery related to the phosphorothioate backbone modification and stimulation of cell mediated immunity is an important component of the invention.

Vollmer et al. (Antisense and Nucleic Acid Drug Development 12:165-175, 2002) was previously cited for the teaching that "non-CpG T-rich ODNs are always less efficient and potent than CpG ODNs", and that the mechanism of action by non-CpG "remains to be elucidated". Understanding mechanism is not a prerequisite to patentability. Applicant again points out that the results of Vollmer et al. are dosage-specific and that there is an optimal dose for activity of T-rich nucleic acid which may not be reflected in the data of Vollmer et al. In support thereof, the Examiner is directed to Figure 1 of Vollmer et al. which shows immunostimulation by a T-rich nucleic acid that is 17 nucleotides in length (ODN 5192). The dose-response data for this nucleic acid demonstrate that its stimulatory capacity increases substantially with increasing dose. The data highlighted by the Examiner in Figure 2 of Vollmer et al. corresponds to a single dose and there is no indication that it is necessarily the optimal dose for the nucleic acids tested. Additionally, the fact that phosphorothioate nucleotide analogs may be less immunostimulatory than CpG ODNs under some conditions is not relevant to patentability. Applicant need only show that the claimed method achieves its intended result, not that it achieves a better result than other methods. Applicant has met this burden by demonstrating that phosphorothioate nucleotide analogs are immunostimulatory. Applicant respectfully disagrees with the Examiner that Vollmer et al supports the Examiner's assertion of unpredictability.

Mojcik et al. (Clinical Immunology and Immunopathy 67(2): 130-136, 1998), Branda et al. (Biochemical Pharmacology 45(10):2037-2043, 1993), and McIntyre et al. were cited as teaching that "induction of splenomegaly and stimulation of B-lymphocyte proliferation in mice injected

with phosphorothioate oligos occurs unpredictably in a manner that is dependent on the nucleotide sequence of the phosphorothioate oligonucleotide analogs." The Examiner has not presented evidence to support this broad conclusion that this was known or widely accepted in the art at the time the instant application was filed. Each of these references represents a very small number of examples and the effects may be explained by antisense activity.

Liang et al. (J. Clin. Invest 98(5): 1110-1129, 1996) was cited as teaching that although "certain oligodeoxynucleotides can stimulate murine B cells, much less information is available on the immunostimulatory capacity of these materials for human B cells" and that "it is not possible to extrapolate results obtained from mouse to man". However, the instant specification provides examples that demonstrate the ability of the phosphorothioate oligonucleotide analogs to induce an immune response in mice (Example 8), rats (Example 7) as well as humans (Examples 9 – 11).

Reconsideration and withdrawal of the rejection is respectfully requested.

Objections to the Specification

The objection to the specification as failing to provide antecedent basis for the phrase "wherein the phosphorothioate oligonucleotide is non antisense" has been maintained. The rejection has been maintained because the specification "does not use either the terms 'sense' or 'not antisense' in describing the analogs of the invention." (Office Action page 3) It is also pointed out that the specification on page 10 lines 16-18 describes phosphorothioate antisense analogs.

It is not necessary for establishing support for claim terms that the exact words "not antisense" appear in the specification. It is required that "each claim limitation must be expressly, implicitly, or inherently supported in the originally filed disclosure." MPEP 2163.05. When the specification provides a teaching that the oligonucleotide may have antisense activity, it is implied that it may not have antisense activity. If the oligonucleotide does not have antisense activity it is not an antisense oligonucleotide. Antisense oligonucleotides function by binding to a complementary RNA sequence and preventing production of a protein. The function of antisense oligonucleotides is dictated by the structure. The primary structure of an antisense oligonucleotide, the nucleotide sequence, determines whether the oligonucleotide is complementary to an RNA. The

fact that applicant has taught in the specification that the oligonucleotides can work independent of an antisense method, clarifies that the invention is not limited to antisense oligonucleotides.

As stated in applicant's prior response paragraph 0016 of the specification teaches "It has now been found, surprisingly, that oligonucleotide analogs having at least one phosphorothioate bond can induce stimulation of a local immune response. *This immunostimulation does not appear to be related to any antisense effect which these oligonucleotide analogs may or may not possess.*" emphasis added. The term cannot lack antecedent basis in the specification, when it is an important part of the discovery of the invention. The term is implicitly supported in the specification.

Accordingly, withdrawal of the rejection of claims 1, 5, 8-14, 20-33 and 35 under 35 U.S.C. §112 is respectfully requested.

Double Patenting Rejection

Claims 26, 28, 29 and 30 have been rejected as being unpatentable over claims 1-8 of U.S. Patent 6,727,230 (Hutcherson, et al.) in view of U.S. Patent 5,356,882 (Walker, et al.)

Stated again for the record, applicants may consider filing a Terminal Disclaimer if some claims are found to be allowable. It is respectfully requested that the rejection be delayed until claims are found to be allowable.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. C1037.70049US00.

Dated: August 14, 2008

Respectfully submitted,

By _____

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